Application No: 09/805,761 Docket No.: VASG-P03-003
Reply to Office Action of November 27, 2007

REMARKS/ARGUMENTS

Claims 1-5, 8-11, 14, and 19-25 are pending in the subject application.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Claim Rejections under 35 U.S.C. § 103(a)

The Examiner continues to reject claims 1-4, 8-11, 14, 19-21, and new claims 22-25 as being allegedly obvious over Uchida et al. (U.S. 6,150,092) in view of Robinson et al. (WO 95/04142), Agrawal et al. (*PNAS*, 94:2620-2625, 1997), and Bennett et al. (U.S. 5,998,148). Applicants respectfully traverse this rejection. Applicants note that the Examiner's rejection of claims 22-27 should be made against claims 22-25.

Applicants maintain the arguments already made of record and contend that the cited references do not render the claims obvious. As an initial matter, the Examiner continues to inaccurately imply that Uchida discloses SEQ ID NO: 7 as *the* "core region." Contrary to the Examiner's assertion, Uchida teaches a *much larger* core region than SEQ ID NO: 7. Uchida's core regions span at least about 500 nucleotides in the VEGF gene (see the paragraph bridging columns 20 and 21), including regions within the 77- to 570-positions in SEQ NO: 1, the nucleotide sequences from the 95- to 108-positions (SEQ ID NO:2), 149- to 174-positions (SEQ ID NO:3), 185- to 210-positions (SEQ ID NO:4), 219- to 244-positions (SEQ ID NO:5), 254- to 276-positions (SEQ ID NO:6), 287- to 328-positions (SEQ ID NO:7), 357- to 372-positions (SEQ ID NO:8), 389- to 534-positions (SEQ ID NO:9), SEQ ID NOS:2, 4, 5, 6, 7, and 9 (see column 21, lines 34-49), all of which are referred to as "core regions".

In contrast, the claimed invention relates to a *particular* VEGF antisense oligonucleotide, i.e., SEQ ID NO: 34. Although Uchida discloses *hundreds* of antisense oligonucleotides, Uchida does not disclose the claimed nucleotide sequence. The teachings of Uchida, at best, disclose a *genus* of VEGF antisense oligonucleotides which target the large "core regions" spanning over 500 bps, while the claimed nucleotide sequence essentially constitutes a *species* invention.

MPEP 2144.08, Section II.A.4 sets forth the guideline for determining whether a claimed species is obvious in view of a prior art genus: "[i]n light of the findings made relating to the

three *Graham* factors, Office personnel should determine whether one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, *i.e.*, to select the claimed species or subgenus from the disclosed prior art genus. *See, e.g., Ochiai*, 71 F.3d at 1569-70, 37 USPQ2d at 1131; *Deuel*, 51 F.3d at 1557, 34 USPQ2d at 1214 ('[A] *prima facie* case of unpatentability requires that the teachings of the prior art suggest the claimed compounds to a person of ordinary skill in the art.' (emphasis in original)); *Jones*, 958 F.2d at 351, 21 USPQ2d at 1943-44 (Fed. Cir. 1992); *Dillon*, 919 F.2d at 692, 16 USPQ2d at 1901; *In re Lalu*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984) ('The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound.')...To address this key issue, Office personnel should consider all relevant prior art teachings, focusing on" (where applicable) (a) the size of the genus, (b) the express teachings, (c) the teachings of structural similarity, (d) the teachings of similar properties or uses, (e) the predictability of the technology, and (f) any other teaching to support the selection of the species or subgenus.

Applicants maintain that the claimed species invention is not obvious in view of Uchida's disclosure. Uchida provides no teaching or suggestion to select the claimed species sequence. Regarding the "size of the genus" factor, a skilled artisan would know that Uchida's genus disclosure of the "core region" (over 500-bp in length) encompasses at least *thousands* of species antisense sequences directed to this "core region," considering that each antisense oligonucleotide may differ from each other by at least one nucleotide and by length. In contrast, the claimed invention only relates to a single specific species sequence. The large size of the genus clearly favors the non-obviousness of the claimed invention, particularly in the absence of any teachings of Uchida to select the claimed species sequence.

Regarding the "teachings of similar properties or uses" factor, Applicants note that it is the instant specification that discloses the unexpected result of using the claimed antisense sequence (SEQ ID NO: 34, referred to as "AS3") to achieve substantial inhibition of cancer cell proliferation in cultured cells and in animal models (see, e.g., Examples 13-17 on pages 56-67).

Finally, in considering the "predictability of the technology", this consideration also favors non-obviousness in this case because antisense technology was well known for its unpredictability. Indeed, VEGF antisense oligonucleotides differing by one or two nucleotides

exhibit significantly different activity in inhibiting VEGF expression. For example, Uchida's Table 2 shows that although A473J differs from A473I by a single nucleotide, there is an approximately 50-fold difference in their activities. Also, Applicants' specification discloses that although SEQ ID NOs: 8 and 9 differ by two nucleotides, there is about a 10-fold difference in their activities (see Table 1 on page 24). In addition, Table 5B shows two mutant sequences (AS-3 mut 1 and AS-3 mut 2) which differ from the AS-3 sequence (i.e., the claimed SEQ ID NO: 34 sequence) by only one or two nucleotides. Despite the minor difference in sequence, the AS-3 (SEQ ID NO: 34) is remarkably more potent than the two mutant sequences (mut 1 and mut 2) at various concentrations examined, both in in vitro and in vivo experiments (see, e.g., Figures 16A and 22). Indeed, the present application shows that SEQ ID NO: 34 inhibits VEGF expression better than other similar sequences, an *unexpected* result that could not have been predicted from the cited art.

The Examiner appears to focus on the "structural similarity" (i.e., sequence similarity) factor. However, Applicants submit that the claimed antisense nucleotide sequence is a distinct molecule having a unique nucleic acid sequence. In view of the unpredictable characteristics of antisense molecules and the unexpected results of the claimed sequence of SEQ ID NO: 34, it is clear to one of skill in the art that structural similarity does not predict functional similarity in the field of antisense technology. By considering all the relevant factors, the *totality* of the circumstances strongly favors the non-obviousness of the claimed species sequence.

Furthermore, Applicants traverse the Examiner's assertion that Uchida would motivate one of ordinary skill in the art to test a myriad of probes within the region corresponding to Uchida's SEQ ID NO:7 so as to arrive at the presently claimed sequence and use this particular antisense probe in methods for inhibiting tumor grwoth and for inhibiting angiogenesis effectively in vivo. Moreover, the defects of Uchida cannot be cured by the other cited references (Robinson, Agrawal, and Bennett) in any combination since the other cited references simply fail to provide any sequence that is identical or similar to the claimed sequence. The Examiner's position relies on the unfounded conclusion that Uchida presents data that would be persuasive to one of ordinary skill in the art. In order to arrive at the presently claimed invention, one of ordinary skill in the art would need to change the sequence of one of the antisense probes described by Uchida and, further, introduce phosphorothioate modifications. However, as noted in the previously submitted Declarations under 37 CFR 1.132 from Dr. Gill

and Dr. Zhang, Uchida's disclosure does not provide any rational basis for designing the claimed antisense probe which is phosphorothioate-modified and intended for use in vivo.

According to the Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 In View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* (Federal Register Vol. 72, No. 195 at pages 57,526-57,535) (effective October 10, 2007) ("the Guidelines"), a § 103 claim rejection based on a purported teaching, suggestion or motivation to combine prior art references to arrive at the claimed invention must support a conclusion of obviousness by including: (1) a finding that there was some teaching, suggestion or motivation to modify or combine the cited references; (2) a finding that there was a reasonable expectation of success; and (3) whatever additional findings based on the *Graham* factual inquiries may be necessary in view of the specific facts.

Applicants reiterate for the reasons already made of record and the reasons as outlined above that the Examiner has not satisfied the requirements of establishing a *prima facie* case of obviousness against independent claims 1 and 8, which require a distinct and specific nucleotide sequence of SEQ ID NO: 34 (modifed form of SEQ ID NO: 2). Applicants also reiterate for the reasons already made of record and the reasons as outlined above that the Examiner has not satisfied the requirement of establishing a *prima facie* case of obviousness against independent claims 9 and 22 which are directed to methods for inhibiting tumor growth and angiogenesis ***in vivo*** by utilizing SEQ ID NO: 34.

In summary, the combined teachings of Uchida and the other cited references (Robinson, Agrawal, and Bennett) fail to establish a *prima facie* case of obviousness. First, because the claimed antisense sequence is distinct from any of the Uchida's sequences, one of skill in the art would not have been motivated to modify Uchida's sequence to arrive at the claimed SEQ ID NO: 34. Second, even were there motivation to make such a substitution, one of skill in the art would have understood that an antisense oligonucleotide does not necessarily functionally translate to an effective sequence. Finally, the unexpected results associated with the particular sequence now being claimed amply demonstrate the non-obviousness of the presently claimed subject matter.

Accordingly, Applicants submit that all of the pending claims are non-obvious in view of the cited references. Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 USC § 103.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000. If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945,** under Order No. **VASG-P03-003.**

Dated: May 27, 2008

Respectfully submitted,

By _____

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